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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/813,398	03/20/2001	Bruce D. Weintraub	UOFMD.003C1	2940

7590 12/12/2002

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EXAMINER	
SPECTOR, LORRAINE	

ART UNIT	PAPER NUMBER
1647	14

DATE MAILED: 12/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 10/2/02

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-19 is/are pending in the application.
Of the above, claim(s) 3, 4, 8-19 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1, 2, 5-7 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☒ Claim(s) 1-19 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☒ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 10
☒ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

Part III: Detailed Office Action

Restriction Requirement:

Applicant's election with traverse of species CGβ with a further election of species of CGβ N77B in Paper No. 13, files 10/2/02 is acknowledged. The traversal is on the ground(s) that the requirement "unnecessarily limits the definition of Applicants invention". This is not found persuasive because the issue here is that the four members of the glycoprotein hormone family each require separate search and consideration, and that to search the full breadth of the claims would place an undue search burden on the Examiner. Further, every single claimed substitution requires separate consideration of the art and application of appropriate art rejections, which also would be a burden to the Examiner. Applicants are correct in their assertion that *if* the generic claim were indicated to be allowable, that all claimed species would also be examined.

The requirement is still deemed proper and is therefore made FINAL.

In a telephone call on 12/9/02, attorney Patrick Delaney requested that species V79B be examined rather than the originally elected species N77B. It is noted that V79B is referred to in claim 6 as V80B; only the art-conventional numbering (V79B) will be used for the remainder of this Office Action. The Examiner agreed, and that is the species that is elected and considered herein.

Claims 1, 2 and 5-7 are under consideration. The remaining claims are withdrawn from consideration as being drawn to non-elected species, there being no allowable generic claim.

Formal Matters:

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing

Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant is required to comply with the sequence rules, 37 CFR 1.821 - 1.825 within the shortened statutory time period set forth for response to this Office Action. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for response beyond the SIX MONTH statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

The disclosure is objected to because of the following informalities: The disclosure should be carefully reviewed for typographical errors. For example, at page 5, line 10, "hCH" should read --hCG--.

Appropriate correction is required.

Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2 and 5-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "increased bioactivity" in claim 1 is a relative term which renders the claim indefinite. The term "increased bioactivity" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. In this case, it is noted, for example, that by making only 8 substitutions in hCG, including N77D, one can generate hLH, which would have 'increased' LH 'bioactivity'. Accordingly, the claim fails to particularly point out that which

applicant regards as the invention.

Because of the improper numbering of the sequence of SEQ ID NO: 3, which is the reference sequence given for hCGβ, only some of the recited residues in claim 6 exist, and the claim is indefinite. It is further noted that the claim is internally inconsistent, for example "N77B" corresponds to art-accepted numbering, while "V80B" corresponds to the numbering of SEQ ID NO: 3. For the purpose of applying the prior art, the claims will be interpreted using the art-accepted numbering.

The remaining claims are rejected for depending from an indefinite claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2 and 5-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specific species listed in the below rejections under 35 U.S.C. § 102, does not reasonably provide enablement for the breadth of species claimed, which are claimed to have "increased bioactivity". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The specification asserts, and the claims require, that the claimed proteins have increased bioactivity. It is noted that the term itself is indefinite in this context, see above. However, the specification provides no guidance as to which species would be expected to have increased

bioactivity, and there is not a single working example of an hCG mutein that has increased bioactivity. While it would not be undue experimentation to make and test each of the specifically claimed species, it is not predictable which species do or do not meet the limitations of the claims, and for those species that do not possess the required activity, the specification has not taught how to make such species have the required activity. The state of the art is that numerous muteins of glycoprotein hormones are known, however it is not recognized in the art as being predictable how one might expect to increase the biological activity of such, in particular by changing the charge distribution, as is claimed in this case. Further, there is not guidance as to which activity or activities can be increased, nor when to expect which. Accordingly, enablement is not commensurate in scope with the species listed in claim 6, and enablement is not commensurate in scope with claims to any human glycoprotein hormone comprising at least one electrostatic charge altering mutation in a β hairpin loop structure, said protein having increased bioactivity.

Rejections Over Prior Art:

Priority Determination: PCT/US98/19772 does not evince the concept of "an electrostatic charge altering mutation in a β hairpin loop structure" of a glycoprotein hormone family member, but rather is drawn to specific mutations in TSH. Further, there is no conception therein of the specifically claimed hCGβ muteins. Accordingly, priority for the claims under consideration is set at 3/19/99.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2 and 7 are rejected under 35 U.S.C. 102(a) as being anticipated by Moyle, WO 98/58957.

Moyle discloses disulfide cross-linked glycoprotein hormone analogs. Such cross-linking meets the limitation of claim 7. Species R8C (Figure 34B) meets the limitation of having a charge-altering mutation, and is disclosed as having prolonged bioactivity, see page 83. C-uncharged

Claims 1, 2, 5 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Lund et al., WO97/04098. Lund et al. disclose hCG muteins. Mutants 2, 7-10 and 20 all meet the limitation of having 'charge altering' mutations, and all have reduced binding to LH cross-reactive antibodies, thus meeting the limitation of having 'increased bioactivity', as a GC-specific vaccine. Mutant 10 of Lund et al. is the elected species, V79B, having a histidine inserted at that locus.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Campbell et al., WO91/16922. Campbell et al. constructed multiple muteins of hCG, incorporating residues from LH; see Table 6, page 65. Substitutions N77D and V55K are charge-altering substitutions. Campell et al. are silent with respect to any 'increased bioactivity' that might be exhibited by the muteins. Because of that, and because of the uncertainty as to what 'increased bioactivity' requires, the Examiner cannot determine whether the muteins of Campbell et al. meet the limitation of having 'increased bioactivity'. With these conditions, where the product seems to be identical except that the prior art is silent to the characteristic or property claimed, then the burden shifts to applicant to provide evidence that the prior art would *neither* anticipate *nor* render obvious the claimed invention. Note the case law of *In re Best* 195 USPQ 430, 433 (CCPA 1977).

Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell et al., WO91/16922, in view of Boime et al., U.S. Patent Number 6,242,580.

The teachings of Campbell et al. are summarized above. Campbell et al. do not teach or suggest a single chain molecule comprising the altered β subunits.

Boime et al. teach single chain forms of the glycoprotein hormone quartet, which includes hCG. Advantages of such include increased stability, and advantages for recombinant expression, especially in bacteria; see column 4, lines 30-36, for example.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to have modified the altered hCG disclosed by Campbell, expressing such as single chain constructs comprising an α subunit and the altered β subunit, in view of Boime's teaching of methods and advantages of doing so. Accordingly, the invention, taken as a whole, is *prima facie* obvious over the prior art.

Advisory Information:

No claim is allowed.

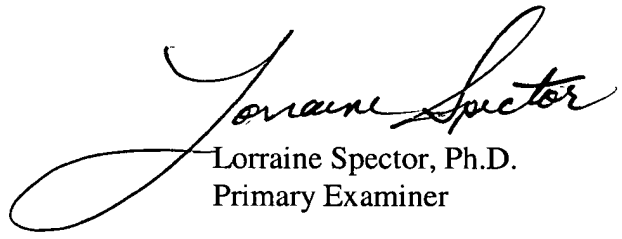
Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 5:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary L. Kunz, at (703)308-4623.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 872-9306 (before final rejection) or (703)872-9307 (after final). Faxed draft or informal communications with the examiner should be directed to (703) 746-5228.



Lorraine Spector, Ph.D.
Primary Examiner

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12/10/02